

Preintervention Arterial Remodeling Affects Clinical Outcome Following Stenting: An Intravascular Ultrasound Study

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OBJECTIVES	The study was done to elucidate the relationship between baseline arterial remodeling and clinical outcome following stenting.
BACKGROUND	The impact of preintervention arterial remodeling on subsequent vessel response and clinical outcome has been reported following nonstent coronary interventions. However, in stented segments, the impact of preintervention remodeling on clinical outcome has not been clarified.
METHODS	Preintervention remodeling was assessed in 108 native coronary lesions by using intravascular ultrasound (IVUS). Positive remodeling (PR) was defined as vessel area (VA) at the target lesion greater than that of average reference segments. Intermediate or negative remodeling (IR/NR) was defined as VA at the target lesion less than or equal to that of average reference segment. Remodeling index expressed as a continuous variable was defined as VA at the target lesion site divided by that of average reference segments.
RESULTS	Positive remodeling was present in 59 (55%) and IR/NR in 49 (45%) lesions. Although final minimal stent areas were similar (7.76 ± 1.80 vs. 8.09 ± 1.90 mm ² , $p = 0.36$), target vessel revascularization (TVR) rate at nine-month follow-up was significantly higher in the PR group (22.0% vs. 4.1%, $p = 0.01$). By multivariate logistic regression analysis, higher remodeling index was the only independent predictor of TVR ($p = 0.02$).
CONCLUSIONS	Lesions with PR before intervention appear to have a worse clinical outcome following IVUS-guided stenting. Intravascular ultrasound imaging before stenting may be helpful to stratify lesions at high risk for accelerated intimal proliferation. (J Am Coll Cardiol 2001;37:1031-5) © 2001 by the American College of Cardiology

Patterns of adaptive vessel remodeling during the course of plaque development have been shown to play an important role in both the progression of de novo atherosclerosis (1-3) and in the restenotic process following coronary interventions (4,5). Recently, intravascular ultrasound (IVUS) studies have demonstrated that patterns of remodeling are associated with both clinical presentation (6-8) and long-term outcome following nonstent coronary interventions (9-11). Several reports have suggested extreme remodeling associated with large plaque burden represents biologically active disease that may not be particularly well suited to intervention (7,9,11,12).

Stenting has become the dominant endovascular strategy for symptomatic coronary artery disease, preventing chronic vessel shrinkage and blunting a major component of the restenotic process following nonstent interventions. However, it is not known whether remodeling before intervention affects clinical outcome following stent implantation. The aim of this study was to assess the impact of remodeling

on clinical outcome following IVUS-guided stent implantation.

METHODS

Patient and lesion criteria. A total of 161 lesions with both pre- and postintervention IVUS imaging were enrolled from 499 patients of the original CRUISE (Can Routine Ultrasound Influence Stent Expansion) study cohort. Inclusion criteria and primary results of the CRUISE study have been reported previously (13). Briefly, patients with symptomatic ischemic heart disease of native coronary circulation were included. Elective stenting with up to two stents (Palmaz-Schatz stents only) were deployed per patient. The use of IVUS was assigned on a center-by-center basis, with seven centers assigned to an angiographic-guidance alone and nine centers assigned to both angiographic- and IVUS-guided groups. Target vessel revascularization (TVR) rates were independently evaluated at nine months.

Of the 161 lesions, 24 lesions were excluded because of severe target lesion calcification, 29 lesions were also excluded because either the proximal or distal reference segment was not available and precluded accurate assessment of target vessel remodeling. Finally, a total of 108 lesions from 108 patients with *both* pre- and postintervention IVUS imaging were included for analysis in the study.

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Abbreviations and Acronyms

CRUISE	= Can Routine Ultrasound Influence Stent Expansion study
IR/NR	= intermediate or negative remodeling
IVUS	= intravascular ultrasound
LA	= lumen area
MLD	= minimal lumen diameter
PA	= plaque area
PR	= positive remodeling
SD	= standard deviation
TVR	= target vessel revascularization
VA	= vessel area

Quantitative coronary angiography. Angiography was digitized and analyzed by the independent core laboratory in Washington Hospital Center (Washington, D.C.) using an automated edge-detection algorithm (CAAS-II, Maastricht, The Netherlands). The minimal lumen diameter (MLD) and reference diameter were used to calculate the percent diameter stenosis.

Ultrasound imaging protocol. A commercially available system (CVIS/Boston Scientific, San Jose, California) was used for IVUS examination. The system consisted of a single-element 30-MHz transducer mounted on the tip of a flexible shaft and rotating at 1,800 rpm within a 2.9 F rapid exchange/common distal lumen imaging sheath, or within a 3.2 F short monorail imaging sheath. Intracoronary nitroglycerin (200 μ g) was given prior to angiogram and repeated within 5 min of IVUS catheter imaging sequence. The IVUS imaging was performed before intervention and repeated after stenting. Ultrasound images were recorded on half-inch (1.27 cm) Super-VHS videotape for off-line analysis.

Quantitative ultrasound. All ultrasound images were evaluated by a core laboratory at Stanford University Medical Center (Stanford, California). The images were digitized to perform morphometric analysis with commercially available planimetry software (TapeMeasure™, Indec Systems, Mountain View, California). Morphometric parameters consisted of vessel area (VA) and lumen area (LA). The VA was defined as the area within the medial/adventitial border (that is, including lumen, plaque and media). Plaque area (PA) was calculated as VA minus LA or stent area.

The IVUS measurements were performed at the tightest segment within the stent and the proximal and distal reference segments (defined as the location with the least amount of disease within 10 mm of the stent border without intervening branches). Patterns of remodeling were classified into two categories: 1) positive remodeling (PR) was defined as VA at the target lesion greater than that of the average reference segments, and 2) intermediate or negative remodeling (IR/NR) was defined as VA at the target lesion less than or equal to that of average vessel reference segments. Remodeling index was calculated as VA at the target lesion divided by the average of the vessel reference segments (Figs. 1 and 2).

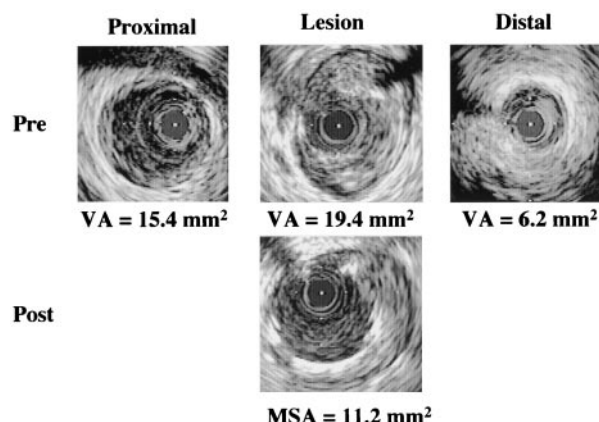


Figure 1. Representative IVUS images of a lesion with PR before intervention. After stenting, MSA of 11.2 mm² was obtained with IVUS guidance. IVUS = intravascular ultrasound; MSA = minimal stent area; PR = positive remodeling; VA = vessel area.

Clinical follow-up. The clinical follow-up was obtained at nine months following stenting for the occurrence of TVR; the TVR was defined as clinically driven repeat revascularization of the initially treated target vessel. Clinical data were independently adjudicated at the Cardiovascular Data Analysis Center at the Beth Israel Deaconess Medical Center (Boston, Massachusetts).

Statistical analysis. Quantitative data were presented as a mean value \pm SD, and qualitative data as frequencies. Continuous variables were compared using unpaired *t* tests. Binary variables were examined by use of the Fisher exact test and chi-square test. To identify predictors of TVR, multivariate logistic models were used. Variables entered into the logistic models were those with a univariate probability value of *p* < 0.20. Statistical significance was a value of *p* \leq 0.05. All statistical analyses were performed with SPSS version 6.1.

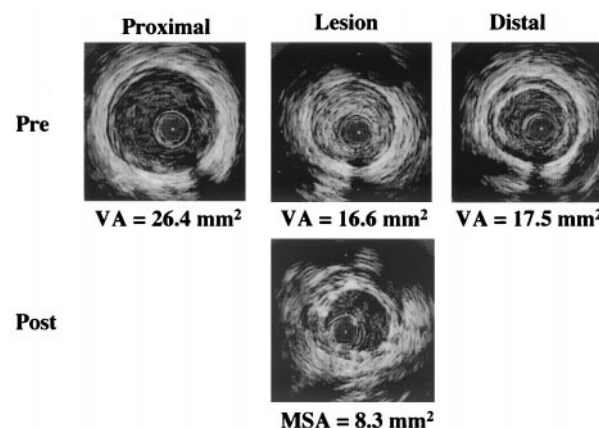


Figure 2. Representative IVUS images of a lesion with NR. After IVUS-guided stenting, minimal stent area of 8.3 mm² was achieved. IVUS = intravascular ultrasound; MSA = minimal stent area; NR = negative remodeling; VA = vessel area.

Table 1. Clinical and Lesion Characteristics

	PR (n = 59)	IR/NR (n = 49)	p Value
Age (yrs)	59.6 ± 10.7	59.6 ± 10.1	0.9794
Gender M/F	41/18	33/16	0.8112
Diabetes mellitus, n (%)	14 (24%)	11 (22%)	0.8753
Hypertension, n (%)	26 (44%)	21 (43%)	0.8995
Dyslipidemia, n (%)	30 (51%)	27 (55%)	0.6593
Smoking, n (%)	17 (29%)	16 (33%)	0.6663
Prior myocardial infarction, n (%)	20 (34%)	11 (22%)	0.1904
Prior bypass surgery, n (%)	5 (8%)	5 (10%)	> 0.9999
Target vessel, n (%)			0.2593
LAD	28 (47%)	24 (49%)	
LCX	6 (10%)	10 (20%)	
RCA	24 (41%)	13 (27%)	
ACC/AHA classification, n (%)			0.2715
A	9 (10%)	11 (22%)	
B1	20 (45%)	24 (49%)	
B2	8 (35%)	10 (20%)	
C	4 (10%)	4 (10%)	
Lesion length, mm	11.7 ± 6.3	10.5 ± 5.4	0.3634

ACC/AHA = American College of Cardiology/American Heart Association; IR/NR = intermediate/negative remodeling; LAD = left anterior descending artery; LCX = left circumflex coronary artery; PR = positive remodeling; RCA = right coronary artery.

RESULTS

Patient and lesion characteristics. Preintervention PR was present in 59 (55%) patients, whereas IR/NR was observed in 49 (45%) of 108 patients. As shown in Table 1, no significant differences were seen in clinical characteristics between the PR and IR/NR groups.

Angiographic and IVUS results. Angiographic results are shown in Table 2. Both baseline and postprocedure results were similar between the two groups except for a trend toward a smaller lesion-MLD before intervention in the PR group (1.0 ± 0.3 vs. 1.2 ± 0.4 mm², $p = 0.09$).

Procedural IVUS results are shown in Table 3. Preintervention lesion VA and PA were significantly larger in the PR group (VA: 17.62 ± 5.52 vs. 13.30 ± 3.86 mm², $p < 0.0001$; PA: 14.62 ± 5.74 vs. 10.59 ± 3.40 mm², $p < 0.0001$). In contrast, there was no difference in the LA in each group prior to stenting (3.03 ± 0.49 vs. 3.02 ± 0.59 mm², $p = \text{NS}$). Following stenting, final minimal stent area was similar between the two groups (7.76 ± 1.80 vs. 8.09 ± 1.90 mm², $p = \text{NS}$).

Table 2. Quantitative Coronary Angiography Results

	PR (n = 59)	IR/NR (n = 49)	p Value
Preintervention			
Reference size, mm	3.0 ± 0.5	3.1 ± 0.4	0.3011
Lesion MLD, mm	1.0 ± 0.3	1.2 ± 0.4	0.0877
Lesion DS (%)	65.5 ± 11.2	63.1 ± 11.1	0.2843
Postintervention			
In-stent MLD, mm	2.9 ± 0.4	2.9 ± 0.4	0.4742
In-stent DS (%)	7.1 ± 12.5	7.8 ± 7.1	0.7665

DS = diameter stenosis; IR/NR = intermediate/negative remodeling; MLD = minimal lumen diameter; PR = positive remodeling.

Table 3. Intravascular Ultrasound Results

	PR (n = 59)	IR/NR (n = 49)	p Value
Preintervention			
Vessel area, mm ²	17.62 ± 5.52	13.30 ± 3.86	< 0.0001
Plaque area, mm ²	14.65 ± 5.74	10.59 ± 3.40	< 0.0001
Lumen area, mm ²	3.03 ± 0.49	3.02 ± 0.59	0.9311
Percent plaque area (%)	81.91 ± 13.50	79.16 ± 8.27	0.2161
Remodeling index	1.19 ± 0.18	0.84 ± 0.12	—
Postintervention			
Minimal stent area, mm ²	7.76 ± 1.80	8.09 ± 1.90	0.3617

IR/NR = intermediate/negative remodeling; PR = positive remodeling.

At nine months, the incidence of TVR was significantly higher in the PR group compared to the IR/NR group (22.0% vs. 4.1%, $p = 0.01$). Univariate predictors of TVR with p value < 0.20 were: higher remodeling index ($p = 0.02$), smaller in-stent MLD ($p = 0.14$), smaller final minimal stent area ($p = 0.17$) and a history of smoking ($p = 0.14$). However, by multivariate logistic regression model, the remodeling index was the *only* significant predictor of nine-month TVR ($p = 0.02$).

DISCUSSION

This study demonstrates that the presence of PR before intervention may have a negative impact on clinical outcome following IVUS-guided stent implantation. In addition, this observation is independent of final minimal in-stent dimension, which has been shown to be a critical factor for long-term vessel patency.

Minimal stent area and plaque burden as predictors of clinical outcome after stenting. Several single-center IVUS studies and the multicenter CRUISE trial have shown that minimal stent area is a powerful predictor of both angiographic restenosis and TVR (13–15) following stenting.

Recently, the impact of postprocedural plaque burden on clinical outcome following balloon angioplasty has been reported (16). More recently, plaque burden has been shown to be an important factor related to subsequent in-stent neointimal proliferation. Several reports have addressed the role of preintervention IVUS findings, such as plaque burden and the remodeling pattern, on outcomes following interventions (9,10,17). Recently, a retrospective study demonstrated worse clinical outcome following nonstent interventions for lesions with baseline PR (9). Serial IVUS analysis has shown that lesions with PR have a larger late lumen loss following balloon angioplasty, which may result from their limited PR (vessel compensation) following intervention (10).

Remodeling and in-stent restenosis. In stented lesions, previous studies have demonstrated that the mechanism of restenosis is solely due to in-stent neointimal proliferation without significant contribution of vessel and/or stent recoil (18,19). Therefore, accelerated neointimal growth through

the metallic stent struts in response to overall vessel irritation may be responsible for the unfavorable clinical outcomes observed in the PR vessels. Because PR has been detected more frequently in unstable lesions (6,8), lesions with PR may be more biologically active (9). Several studies have shown that the relative amount of plaque burden outside the stent is related to subsequent neointimal proliferation inside the stent (17,20). An alternative explanation may be the difference in subsequent arterial behavior between lesions with PR and IR/NR. The VA has been shown to increase to compensate for plaque growth outside the stent following stenting (21). Lack of this adaptive remodeling process in lesions with PR may also be responsible for an increasing TVR (10).

Future directions to treat lesions with positive remodeling. Stenting a vessel with large eccentric plaque may require higher expanding force on the “relatively” normal vessel side, causing greater vessel injury and resulting in an increased neointimal response (22). Debulking before stenting (23,24) may improve vessel compliance, reduce force/injury during stent expansion, and ultimately allow appropriate vessel compensation to accommodate plaque growth following stenting. Two randomized trials to assess the efficacy of debulking by directional atherectomy prior to stenting are underway and will probably provide IVUS insights into both short- and long-term behavior of this facilitated technique.

Study limitations. There are several limitations to be mentioned. First, because preintervention IVUS imaging was performed based on each operator’s decision, lesion selection may be biased. In addition, 53 of 161 enrolled lesions (30%) were excluded from the analysis. This exclusion may also bias the result. But to clarify remodeling correctly, pretreatment IVUS scans are necessary. Second, the sample size of this study was relatively small. This may, in part, explain the fact that postprocedure in-stent size was not an independent predictor in this subanalysis. Third, although final minimal stent area was similar between the two groups, stent dimension relative to the VA was smaller in the PR group. Aggressive balloon sizing based on the VA of the lesion might have further improved final lumen dimension and thus better clinical outcome of the positively remodeled lesion. Finally, IVUS imaging was not repeated during follow-up; therefore, the exact mechanism of the higher TVR rate in the PR group is still uncertain.

Clinical implications. Results of the present study suggest that preintervention IVUS imaging may be important prior to stenting. These findings may help stratify lesions at high risk for aggressive intimal hyperplasia in response to stenting. In addition, the significantly higher TVR rates in the PR group, despite the use of IVUS guidance, may suggest the call for adjunctive strategies, such as debulking (23), pharmacologic or radiation therapies (25). Prospective randomized trials specifically targeted to address lesions with positive remodeling should be performed.

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